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(19)

(54) PHARMACEUTICAL PREPARATIONS FOR THE TREATMENT OF HYPERURICACIDEMIA

(71) We, HENNING BERLIN GMBH, of Komturstr. 19—20, 1000 Berlin 42 (Tempelhof), West Germany, a German company,

do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to pharmaceutical preparations for the treatment of hyperuricacidemia.

The two types of drugs mainly employed for treating gout and hyperuricacidemia, namely uricostatic and saluric drugs, have the specific action of lowering the increased level of uric acid in the serum which occurs with this condition. Both groups of drugs lower the elevated concentration of uric acid in the serum to a value below 6.4 mg/100 ml. Whilst the uricostatic drugs inhibit the formation of uric acid, saluric drugs accelerate the excretion of uric acid via the kidneys.

The uricostatic drug most frequently employed is Allopurinol (4 - hydroxy - pyrazolo- (3,4 - d) - pyrimidine) which reduces the amount of uric acid, the final product of the purine metabolism in man, formed in the body by competitive inhibiting action on the enzyme xanthinoxidase. Allopurinol can be given in doses of 100 mg, 3—4 times per day. Recently, administration of a single dose of 300 mg Allopurinol has been recommended. In spite of the fact that Allopurinol has a relatively short biological half life of less than 2 hours, a single dose per day is practicable. In the organism, Allopurinol is rapidly converted to a metabolic product, the so-called 'oxipurinol' (4,6 - dihydroxypyrazolo - 3,4 - d) pyrimidine), by oxidation. 'Oxipurinol' has a comparatively long half life in the organism (about 24 hours) and its impeding action on xanthinoxidase is as strong as that of Allopurinol.

The saluric drug most frequently employed is Benzbromarone ((2 - ethyl - benzofuran- 3 - yl) - (3,5 - dibromo - 4 - hydroxyphenyl) ketone). This is administered in a single dose of 100 mg/day and has a prolonged effect on the excretion of uric acid via the kidneys. The amount of uric acid excreted in the urine per day undergoes a marked increase and this reduces the level of uric acid in the serum. An adequate intake of liquid is of importance in this treatment since there is otherwise a danger of an increase in the concentration of uric acid in the urine which entails the danger of a damage to the kidneys as a result of crystallisation of uric acid in them.

In almost all cases, treatment aimed at reducing the level of uric acid must be continued throughout the remaining life of the patient and the drug employed must, therefore, satisfy specific requirements. The danger of side effects must be reduced to the absolute minimum.

Although both Allopurinol and Benzbromarone are excellent drugs which produce only minor side effects, objections have been raised by various experts to their extensive application in high doses for the permanent treatment of hyperuricacidemia. In the case of Allopurinol warnings have been sounded against its continuous administration in large doses on acount of the unknown effects of this substance of the phosphoribosyl phosphate content (reduction) in the erythrocytes, on the pyrimidine metabolism (inhibition) and on tryptophanpyrrolase (inhibition). Permanent treatment of hyperuricacidemia with Benzbromarone using the customary dose of 100 mg/day has frequently been criticised on account of the danger of damage to the kidneys in cases of failure to observe the necessary high intake of liquids.

The combined application of Allopurinol and Benzbromarone has been recommended as an initial treatment of gout, in particular in cases in which large deposits of uric acid have to be dissolved. It is, however, known that Benzbromarone leads not only to the desired increase in the excretion of uric acid but also to a substantial increase in the excretion of the metabolite oxipurinol, responsible for the prolonged action of Allopurinol. It is, therefore, customary nowadays when using

Allopurinol and Benzbromarone together to administer increased doses of Allopurinol (up to 600 mg). It can be calculated that 50 mg Benzbromarone is equivalent to about 150 mg Benzbromarone together with a 150 mg tioned excretion of oxipurinol a dose of 50 mg Benzbromarone together with a 150 mg dose of Allopurinol would appear to be adequate. However present treatment involves giving 4—6 100 mg doses of Allopurinol and 1—2 doses of Benzbromarone per day.

Surprisingly, however, it has been established that Allopurinol and Benzbromarone display a very marked synergistic effect when administered simultaneously, so that it is possible, in spite of the mentioned increased excretion of oxipurinol, to make do with smaller doses of Allopurinol and Benzbromarone. In cases of hyperuricacidemia still free from symptoms, it is possible to achieve a lowering in the uric acid level with doses of only 75—100 mg Allopurinol and 15—20 mg Benzbromarone which corresponds to the effect achieved with 300 mg Allopurinol or 100 mg Benzbromarone. Thus, using one tablet containing 75 mg Allopurinol plus 15 mg Benzbromarone per day, the uric acid level in the serum of nine patients could be reduced on average by 2.6 mg/100 ml, whilst a tablet containing 100 mg Allopurinol and 20 mg Benzbromarone/day led to a mean reduction by 3.2 mg/100 ml in ten patients.

Accordingly, the present invention provides a pharmaceutical preparation for treating hyperuricacidemia, in the form of a fixed dosage unit for oral administration, wherein the dosage unit contains, in addition to the usual pharmaceutically acceptable excipients, 60—120 mg Allopurinol and 10—30 mg Benzbromarone.

The excipients may include microcrystalline cellulose, highly dispersed silica, a disintegrating agent, a granulating agent and a tabletting lubricant.

The present invention makes it possible to reduce substantially the doses of the active agents given in permanent treatment, which of course at the same time leads to a substantial reduction in the risks that are incurred when medication is carried out with Allopurinol alone or with Benzbromarone alone. Furthermore, the necessity for the patient to take in increased quantities of liquid during the permanent treatment is obviated.

When a patient is given any permanent treatment it is important that the preparation administered is taken as infrequently as possible and in the smallest possible amounts to achieve the desired results. Tablets having a weight of 250—300 mg are sufficiently large to cause many patients difficulty in swallowing. Since the preparations according to the invention contain only about 100 mg total substances, they can be prepared in such a way as to give a tablet having an overall weight of 100—200 mg.

The invention is illustrated by the following examples.

Example 1.

1.00 kg Allopurinol having a mean particle size of 15 μ, 0.20 kg Benzbromarone with a mean particle size ≤ 10 μ are mixed with 0.195 kg microcrystalline cellulose and 0.075 kg sodium carboxymethylamylpectin and the mixture is granulated with an aqueous solution of 0.015 g polyethyleneglycol. After drying, the granulate is mixed with 0.010 kg hydrogenated castor oil and 0.005 kg highly dispersed silica. Using a normal tabletting method, tablets each having a weight of 150 mg are produced.

Each tablet contains the following:

100.0 mg Allopurinol
20.0 mg Benzbromarone
19.5 mg microcrystalline cellulose
7.5 mg carboxymethylamylopectin
1.5 mg polyethylenglycol
0.5 mg silica, highly dispersed
1.0 mg hydrogenated castor oil

The hydrogenated castor oil may be replaced by other tabletting lubricants such as hydrogenated cotton seed oil, stearic acid, magnesium stearate or calcium stearate.

Mixtures of polyvinylpyrrolidone and gelatin or methylcellulose can be used instead of polyethyleneglycol to act as granulating agent. When using polyethyleneglycol and in particular when using polyvinylpyrrolidone, the granulating agent can be mixed with the other ingredients in the dry state and granulation then carried out with water.

Polyvinylpolypyrrolidone can replace sodium carboxymethylamylopectin as the disintegrating agent.

Example 2.

Using the method of Example 1, tablets each having the following composition are prepared:

75.00 mg Allopurinol
15.00 mg Benzbromarone
14.20 mg microcrystalline cellulose
5.60 mg sodium carboxymethylamylopectin
1.10 mg polyethyleneglycol
0.35 mg silica, highly dispersed
0.75 mg hydrogenated castor oil

Each tablet weighs 112 mg.

The same granulating agents, lubricants and disintegrating agents as specified in Example 1 can be used.

The tablets prepared in this manner are distinguished by a rapid disintegration and a fast rate of dissolution.

In all the examples listed the wear fastness and breaking strength were completely satisfactory.

Clinical trials.

Four groups of patients suffering from hyperuricacidemia were treated with preparations which contained either both Allopurinol and Benzbromarone (Table 1) or Allopurinol alone (Table 2).

TABLE 1

Test Conditions	Concentration of uric acid in the serum (mg/dl) (arithmetical mean values with standard deviations) Prior to treatment	After treatment for 8 days
1) 75 mg Allopurinol 15 mg Benzbromarone per day (22 patients)	7.65 ± 1.07	5.17 ± 0.92
2) 100 mg Allopurinol 20 mg Benzbromarone per day (21 patients)	7.38 ± 0.61	4.27 ± 0.84
3) 100 mg Allopurinol 20 mg Benzbromarone per day (12 patients)	6.20 ± 1.32	3.95 ± 1.01
4) 100 mg Allopurinol 20 mg Benzbromarone per day (12 patients)	7.01 ± 1.32	4.27 ± 0.79

Group 4 was treated with Allopurinol alone after the level of uric acid had risen again to the original value.

TABLE 2

Test Conditions	Concentration of uric acid in the serum (mg/dl) (arithmetical mean values with standard deviations) Prior to treatment	After treatment for 8 days
300 mg Allopurinol per day (12 patients)	7.01 ± 1.32	4.72 ± 0.68

The values given in Table 2 correspond to the clinical results observed over a period of years when carrying out treatment with Allopurinol.

That a synergistic effect occurs when Allopurinol and Benzbromarone are administered together is clearly evident from the above tables.

WHAT WE CLAIM IS:—

1. A pharmaceutical preparation for treating hyperuricacidemia in dosage unit form for oral administration, wherein the dosage unit contains in addition to the usual pharmaceutically acceptable excipients 60—120 mg Allopurinol and 10—30 mg Benzbromarone.

2. A preparation according to claim 1 wherein the dosage unit contains 75—100 mg Allopurinol and 15—20 mg Benzbromarone.

3. A preparation according to claim 1 or 2, wherein the dosage unit consists of a tablet

having a weight of 100—200 mg.

4. A preparation according to any one of claims 1 to 3 wherein the inactive constituents comprise microcrystalline cellulose, highly dispersed silica, a disintegrating agent, a granulating agent and a tabletting lubricant.

5. A preparation according to claim 4 wherein the lubricant is hydrogenated castor oil, hydrogenated cotton seed oil, stearic acid, magnesium stearate or calcium stearate.

6. A preparation according to claims 4 or 5 wherein the granulating agent is polyethyleneglycol or mixtures of polyvinylpolypyrrolidone and gelatin or methylcellulose.

7. A preparation according to any one of claims 4, 5 or 6 wherein the disintegrating agent is sodium carboxymethylamylopectin or polyvinylpyrrolidone.

8. A preparation according to claim 1 substantially as herein described with reference to the examples.

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